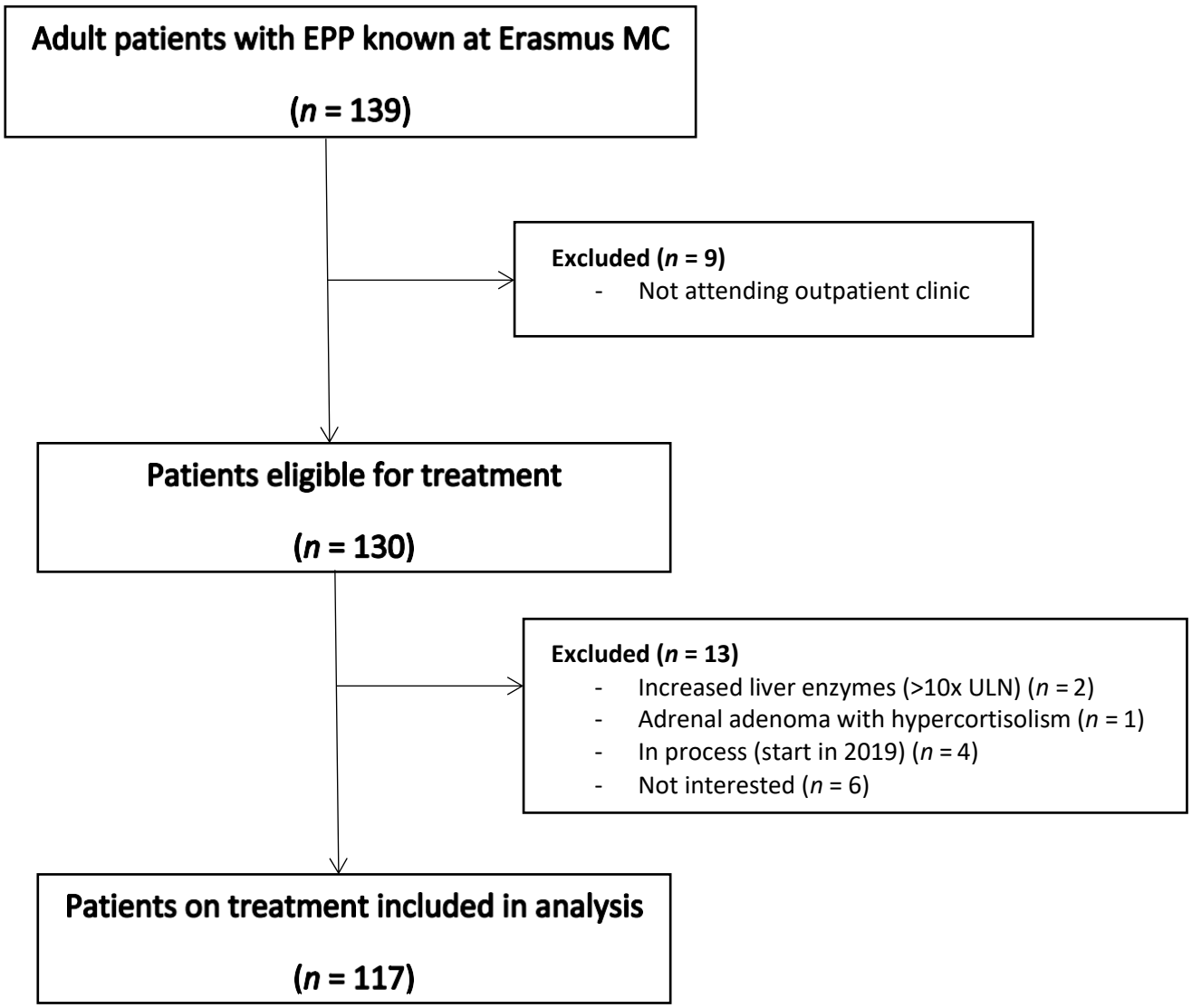
Supplementary Online Content

Wensink D, Wagenmakers MAEM, Barman-Aksözen J, et al. Association of afamelanotide with improved outcomes in patients with erythropoietic protoporphyria in clinical practice. *JAMA Dermatol*. Published online March 18, 2020. doi:10.1001/jamadermatol.2020.0352

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Flowchart inclusion and exclusion of participants



eMethods 1. Overview of used questionnaires

The EPP QoL (eMethods 3): The Dutch translation of the EPP QoL was used. It comprises 12 items regarding general well-being and influence of EPP on daily life measured on a four-point scale. The items are formulated as statements. The frequently used EPP QoL questionnaire is in the process of being validated and is a disease-specific quality of life questionnaire[11,13]. Scores range from 0 to 100, with higher scores indicating better quality of life. Scores are calculated by multiplying the sum of the answers by the factor: total possible answers/number of answer. The EPP Qol was completed during each visit and reflected the past 60 days.

Phototoxic reactions questionnaire (eMethods 4): The questionnaire (non-validated) on phototoxic reactions comprises 5 questions regarding the occurrence of phototoxic reactions, defined as pain occurring in light-exposed skin after light exposure. The duration of the phototoxic reaction is expressed as the total hours of recorded pain during one reaction. Pain is scored on an 11-point Likert pain-intensity scale (with scores ranging from 0 to 10, and higher scores indicating greater severity of pain). This questionnaire was completed during each visit and reflected the previous 60 days.

Sun protection measures questionnaire (eMethods 5):. The questionnaire (non-validated) comprises two items regarding protective clothing. Each protective clothing item is coded with one point, the maximum sun protection score is seven points. The sun protection score questionnaire was completed during each visit and reflected the previous 60 days.

Sunlight score: Objective data on light intensity

EPP is a seasonal disease with more symptoms during spring and summer (high light intensity). We used the sunlight intensity data (global radiation in kJ/cm2) as measured by The Royal Netherlands Meteorological Institute (KNMI). The presented sunlight scores were based on the total global solar radiation per day for the weather station in De Bilt, in the center of the Netherlands. The calculated sunlight score was based on the corresponding days in the questionnaires.

Data management

All data were entered in a database following the PASS protocol, programmed in OpenClinica open source software (version 2.1) (http://www.openclinica.com). The database is hosted within the Erasmus MC, and all EU participating centers register their data anonymously in this OpenClinica database. Each center can enter, and export their own patients records, Clinuvel Pharmaceuticals Ltd. can export all entered data for annual EMA reports on safety and effectiveness. Individual centers, have no access to the data of other centers. An independent database validation check was performed in random 2% of Dutch patients, the error percentage was 1.2%.

Data analysis

Data were summarized using means, median, range and standard deviations for continuous variables and using frequencies and percentages for categorical variables. Baseline values were based on different time points for some variables. For time spent outside baseline values were based on diary information before the first treatment. Other baseline values were based on data collected during the first visit prior to start of the treatment.

Linear mixed modelling was used to estimate the effect of afamelanotide. The effect of afamelanotide treatment was investigated with a linear mixed model with baseline (yes/no), sex, age, BMI, month (December as a reference), sunlight score during the week corresponding with the diary and time since first visit as independent variables. Time spent outside was analyzed separately for week 1 and 5 after treatment. The variable ‘baseline’ was defined as a dichotomous variable with a value 1 for the first measurement (before treatment) and 0 for all later measurements; this variable was used to estimate the intervention effect. The variables age,

BMI, sunlight score and time since first visit were all defined as continuous variables, the variables sex and month were defined as categorical. A random intercept and a random slope of time since first visit were included in all linear mixed models to account for the within- subject correlations. Two-way interaction effects were tested and included in the final model when statistically significant. A square root transformation was applied to the outcome number of phototoxic reactions, in order to obtain a more symmetric and less skewed distribution; no transformations were applied for other outcomes.

Assessment of model residuals supported the underlying assumption of normality. All safety analyses were descriptive, and reported as frequencies and percentages. There were some missing data, not all respondents provided responses to every question. Missing data (only the missing responses) and outliers (values outside of mean ± 4 SD) were excluded from analysis for all variables. Statistical analyses were performed with IBM SPSS statistics for Windows (version 24.0). All statistical tests were two-sided with a significance level of 0.05.

eMethods 2. Daily diary

Patient number:_____Expert centre: _____

POST-AUTHORISATION SAFETY STUDY FOR THE USE OF SCENESSE® (AFAMELANOTIDE 16MG) IN PATIENTS WITH ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

DAILY PATIENT DIARY

Administrative purposes only – For medical staff to complete:

Patient name:							
Patient number:	#	#	#	#	#	#	#
Expert centre number:				#	#	#	#
Diary booklet supplied at Year _____ / Visit _____ Diary Number _____							

Date of receipt of last SCENESSE® implant:	D	D	M	M	M	Y	Y	Y	Y

Staff Initial/Date: _____ /_____

Patient number:_____Expert centre: _____

INSTRUCTIONS FOR FILLING OUT THIS DIARY BOOKLET

- Fill in this diary with a **black** pen. Do not use a pencil or erasable pen.

- **Do not erase data or use correction fluid (liquid paper).** If a correction or alteration is necessary, cross out the original entry with a single line, write the correct information alongside, and initial and date the change.

- This diary will need to be completed **at the end of each day, for up to seven (7) days during the first week and the fifth week after you receive you treatment with SCENESSE® (afamelanotide 16mg)** at Year1/ Visit 1 and all subsequent visits at Year 1 and following years. This is referred to as "Week 1" and "Week 5" in the diary.

- At the end of each day mentioned above**,** you will need to enter the date of the day and complete the following **two (2) sections**:

1. EPP Monitoring

1.1. Indicate by selecting "Yes" or "No" if you have experienced any reaction to light (phototoxicity) today.
If "Yes", go to section 1.2.
If "No", go directly to section 2.

1.2. Circle a number on the scale, from 0 to 10, to indicate your estimate of the severity of the pain related to the reaction experienced today. The number 0 means no pain was experienced from the reaction (it might be other symptoms) while the number 10 means the worst imaginable pain was experienced from this reaction.
Please only circle one number. **If you did not experience any reaction to light (phototoxicity), do NOT circle any number (including 0).**

2. Time Spent Outdoors

2.1. Indicate by selecting "Yes" or "No" if you have spent any time outdoors today.
If "Yes", go to section 2.2.
If "No", do not complete section 2.2, your diary is complete for this day.

2.2. Enter how many hours and minutes you spent outside today.

- **Initial and date your entries** in the space provided once you have finished completing the diary for the day.

- **Bring this diary back to your doctor at your next scheduled visit.** You will be given a new diary to complete.

- **Keep this diary booklet intact and do not remove any pages.**

- **If you lose this diary, please make sure you contact your doctor as soon as possible to obtain a new diary booklet.**

Patient number:_____Expert centre: _____

EXAMPLE PAGE

Daily patient diary – Week 1/Day 1

Date of completion:	1	5	M	A	R	2	0	1	6

1. EPP Monitoring

1.1 Have you experienced any reactions to light (phototoxicity) today? ☐ Yes ☐ No

1.2 If "yes", please indicate on the scale below how bad your pain was from this reaction (circle one number):

0	1	2	3	(4)	5	6	7	8	9	10
No Pain										Worst Imaginable

2. Time Spent Outdoors

2.1 Did you spend any time outdoors today? ☒ Yes ☐ No

2.2 If "yes", how long did you spend outdoors? Hours: 2 Minutes: 25

Patient's Initial/Date: _____ABC__/_15/MAR/2016_

Daily patient diary – Week 1/Day 2

Date of completion:	1	6	M	A	R	2	0	1	6

1. EPP Monitoring

1.1 Have you experienced any reactions to light (phototoxicity) today? ☐ Yes ☒ No

1.2 If "yes", please indicate on the scale below how bad your pain was from this reaction (circle one number):

NOTE: If you selected NO in section 1.1 above, meaning that you did not experience reaction to light (phototoxicity), leave this section blank and complete section 2

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Imaginable

2. Time Spent Outdoors

2.1 Did you spend any time outdoors today? ☐ Yes ☒ No

2.2 If "yes", how long did you spend outdoors? Hours: 0 Minutes: 0

Patient's Initial/Date: _____ABC__/_16 /MAR/2016_

eMethods 3. EPP QoL questionnaire

Patient name:_____Patient number:_____Expert centre:

11a. Quality of Life assessment (EPP-QoL) – Year 1/Baseline

Date of completion of the EPP-QoL	D	D	M	M	M	Y	Y	Y	Y

EPP Quality of Life Questionnaire ("EPP-QoL")

The aim of this questionnaire is to assess the impact of your disease on your quality of life **DURING THE LAST TWO (2) MONTHS**. Please check one box for each question.

1	Over the last two months, how has your well-being been affected by EPP? I have been:	☐ **a)** Much better ☐ **b)** Better ☐ **c)** Same ☐ **d)** Worse
2	Over the last two months, how much has EPP influenced the choice of the clothes you wear on a sunny day?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all
3	Over the last two months, how often did you feel you were at risk of developing EPP symptoms?	☐ **a)** Very often ☐ **b)** Often ☐ **c)** A little ☐ **d)** Not at all
4	Over the last two months, how much has EPP affected any social or leisure activities on a sunny day?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all
5	Over the last two months, how much has EPP influenced your need to plan before leaving your house?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all
6	Over the last two months, has EPP limited your ability to undertake activities in a spontaneous manner?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all
7	Over the last two months, how much has EPP interfered with your going shopping or looking after your home (indoors and outdoors) or garden on a sunny day?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all
8	Over the last two months, how much has EPP prevented you from attending outdoor social activities with family and friends?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all
9	Over the last two months, how much has EPP limited your amount of outdoor activities?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all

(Continued on next page)

Patient's Initial/Date:_____/_____

Patient name:_____ Patient number:_____ Expert centre:

11a. Quality of Life assessment (EPP-QoL) – Year 1/Baseline (continued)

10	Over the last two months, how often did you experience typical EPP skin complaints?	☐ **a)** More than usual ☐ **b)** Same as usual ☐ **c)** Less than usual ☐ **d)** Much less than usual
11	Over the last two months, how much has your quality of life improved?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all
12	Over the last two months, how much has EPP influenced your method of transportation or seating preference during transportation?	☐ **a)** Very much ☐ **b)** A lot ☐ **c)** A little ☐ **d)** Not at all

NB: This EPP specific questionnaire is part of the proprietary knowledge of Clinuvel and therefore cannot be used without the explicit written permission of Clinuvel.

Patient's Initial/Date:_____/_____

eMethods 4. Phototoxic reaction questionnaire

Patient name:_____Patient number:_____Expert centre: _____

7. Phototoxicity (phototoxic reaction review) – Year ____/ Day _____

1. Did the patient experience any reactions to sunlight and/or light sources (phototoxicity) during the last 2 months? ☐ Yes ☐ No

2. How many episodes of phototoxicity did the patient experience during the last 2 months?

_____episodes

[An episode is defined as a flare up/exacerbation occurring during one day or more. There needs to be at least one day of symptom-free existence between each episode to categorize it as two separate episodes]

3. How long did the patient's worst episode of phototoxicity last during this period?

_____days_____hours_____mins

☐ Other (please specify):

4. According to an 11-point Likert scale, how severe was the patient's worse episode of phototoxicity during this period?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Imaginable

5. If the patient had a phototoxic reaction(s), what measure(s) did they take to relieve symptoms?

☐ a) Cold water and/or ice/cold pack
☐ b) Hot water
☐ c) Fans/air conditioning
☐ d) Avoiding all light exposure
☐ e) Avoiding all heat exposure
☐ f) Avoiding sources of pressure
☐ g) Sleeping pills
☐ h) Alcohol

Additional comments on phototoxic reaction review:

_____

_____

_____

_____

_____

_____

Site Staff Initial/Date: _____ /_____

eMethods 5. Sun protection questionnaire

Patient name:_____Patient number:_____Expert centre: _____

6. Sun protection measures – Year ____/ Day _____

Has the patient used measures to protect against light and sun within the last two months? ☐ Yes ☐ No	
Which forms of light and sun protection did the patient use?	
1. Protective clothing	☐ Please select if used
1.1 If protective clothing was used, specify: ☐ a) Hat ☐ b) Balaclava ☐ c) Long sleeves ☐ d) Long trousers ☐ e) Socks ☐ f) Gloves ☐ g) Other (please specify):	
2. Sunscreen	☐ Please select if used
If sunscreen was used, specify:	
• 2.1 Frequency of use	☐ a) Infrequently ☐ b) At least once a week ☐ c) Daily
• 2.2 Trade name	_____ ☐ Or unknown
• 2.3 Composition	☐ a) Physical (reflective sunscreens containing ingredients like zinc oxide, titanium dioxide, ferric chloride and/or iron oxide) ☐ b) Chemical (UV-absorbing sunscreens containing ingredients like parsol, benzophenones and PABA) ☐ c) Unsure
• 2.4 SPF (i.e. 15+, 30+)	_____+
• 2.5 Spectrum	☐ a) UVB only ☐ b) UVA/UVB (broad spectrum) ☐ c) Unsure
• 2.6 Body location of application	☐ a) Face ☐ b) Arms ☐ c) Hands ☐ d) Legs ☐ e) Feet ☐ f) Other (please specify) : _____
3. Environmental adaptations **Visible light filters (polychromatic)** e.g. 1: visors e.g. 2: house windows e.g. 3: car windshields	☐ Please select if used
☐ a) Visors ☐ b) House windows ☐ c) Car windows ☐ d) Other (please specify):	
4. Other forms of light and sun protection	☐ Please select if used
If other forms of light and sun protection were used, provide details:	

Site Staff Initial/Date: _____ /_____

eMethods 6. Secondary endpoints

Daily activity inventory questionnaire

Patient name:_____Patient number:_____Expert centre:

11c. Daily Activity Inventory – Year ____/ Day _____

Date of completion of the Daily Activity Inventory questionnaire	D	D	M	M	M	Y	Y	Y	Y

These questions apply to your experience.

Please tick the box(es) relevant to your answer(s) and complete the fields as required.

Have you received SCENESSE® during the past 2 months? ☐ **Yes** ☐ **No**

If yes, answer all questions. If no, answer questions 1-4 only

1. During the past 2 months, how much did EPP affect your life? (Please choose one answer only)

a) Very much	b) A lot	c) A little	d) Not at all
☐	☐	☐	☐

2. During the past 2 months, on clear/sunny days or indoors under bright lighting, were you able to undertake the activities in the following categories? (Please choose one answer only per activity)

	a) Always	b) Often	c) Sometimes	d) Rarely	e) Not at all	f) Not applicable
2.1 Going to/from work/school	☐	☐	☐	☐	☐	☐
2.2 Caring for family members, friends or pets	☐	☐	☐	☐	☐	☐
2.3 Activities at work/school	☐	☐	☐	☐	☐	☐
2.4 Shopping for daily requirements	☐	☐	☐	☐	☐	☐
2.5 Gardening	☐	☐	☐	☐	☐	☐
2.6 Walking for leisure	☐	☐	☐	☐	☐	☐

	a) A lot	b) A little	c) Sometimes	d) Rarely	e) Not at all	f) Not applicable
2.7 Outdoor sports	☐	☐	☐	☐	☐	☐
2.8 Indoor sports	☐	☐	☐	☐	☐	☐

(Continued on next page)

Patient's Initial/Date: _____ /_____

Taking measures score questionnaire

Patient name:_____Patient number:_____Expert centre:

11c. Daily Activity Inventory – Year ____/ Day_____ (continued)

3. During the past 2 months, how often did you take the following measures before going outside? (Please choose one answer only per category)

	a) Always	b) Often	c) Sometimes	d) Rarely	e) Never	f) Not applicable
3.1 Checking the weather or the forecast	☐	☐	☐	☐	☐	☐
3.2 Checking, planning the time of day, if problematic weather is present or expected	☐	☐	☐	☐	☐	☐
3.3 Checking, planning the route to the destination, if problematic weather is present or expected	☐	☐	☐	☐	☐	☐
3.4 Carrying protective clothing (and putting on when needed)	☐	☐	☐	☐	☐	☐

4. During the past 2 months, how often did you wear the following clothing to protect your skin from outdoor light and/or indoor lighting? (Please choose one only per category)

If you use other measures, please specify where indicated.

	a) Always	b) Often	c) Sometimes	d) Rarely	e) Never
4.1 Hat	☐	☐	☐	☐	☐
4.2 Balaclava/face and neck protecting cap	☐	☐	☐	☐	☐
4.3 Long sleeves	☐	☐	☐	☐	☐
4.4 Long trousers/skirts	☐	☐	☐	☐	☐
4.5 Socks/tights	☐	☐	☐	☐	☐
4.6 Gloves	☐	☐	☐	☐	☐
4.7 No protective clothing	☐	☐	☐	☐	☐
If other, please specify					

(Continued on next page)

Patient's Initial/Date: _____ /_____

Symptoms after light exposure

Patient name:_____Patient number:_____Expert centre:

11c. Daily Activity Inventory – Year ____/ Day _____ (continued)

Self-confidence score

5. During the past 2 months, how often did you experience skin symptoms (phototoxicity) after light exposure? (Please choose one only)

a) Always	b) Often	c) Sometimes	d) Rarely	e) Never
☐	☐	☐	☐	☐

6. How often did the following statements apply to how EPP affects your life during the past 2 months? (Choose one answer per question)

	a) Always	b) Often	c) Sometimes	d) Rarely	e) Never
6.1 Makes me less self-confident:	☐	☐	☐	☐	☐
6.2 Makes me more anxious:	☐	☐	☐	☐	☐
6.3 Forces me to live a solitary life:	☐	☐	☐	☐	☐
6.4 Makes me depressed:	☐	☐	☐	☐	☐
6.5 Makes me angry:	☐	☐	☐	☐	☐
6.6 Makes me disappointed about life:	☐	☐	☐	☐	☐
6.7 Makes me feel different to others:	☐	☐	☐	☐	☐

7. During the past 2 months, how has EPP affected your immediate family?
(Please choose one only) Influence of EPP on family

a) Very much	b) A lot	c) Somewhat	d) Not at all
☐	☐	☐	☐

8. How much did EPP affect your activities during the past season? (Please choose one answer only for the relevant season)

	a) Very much	b) A lot	c) Somewhat	d) Not at all
8.1 Spring	☐	☐	☐	☐
8.2 Summer	☐	☐	☐	☐
8.3 Autumn	☐	☐	☐	☐
8.4 Winter	☐	☐	☐	☐

(Continued on next page)

Patient's Initial/Date: _____ /_____

Patient name:_____Patient number:_____Expert centre:

11c. Daily Activity Inventory – Year ____/ Day _____ (continued)

9. During the past 2 months, how much light were you been able to tolerate without experiencing symptoms during your leisure time? (Please choose one only)

a) Much more than before SCENESSE®	b) More than before SCENESSE®	c) A little more than before SCENESSE®	d) Same as before SCENESSE®	e) Less than before SCENESSE®
☐	☐	☐	☐	☐

10. During the past 2 months, how often were you anxious/ fearful/ worried about experiencing skin symptoms following light exposure? (Please choose one only)

a) Always	b) Often	c) Sometimes	d) Rarely	e) Never
☐	☐	☐	☐	☐

11. During the past 2 months, how often have you been inclined to go outdoors on a clear/sunny day? (Please choose one answer only)

a) Much more than before SCENESSE®	b) More than before SCENESSE®	c) A little more than before SCENESSE®	d) Same as before SCENESSE®	e) Less than before SCENESSE®
☐	☐	☐	☐	☐

12. How do you assess your ability and willingness to go outdoors on a clear/sunny day during the past 2 months? (Please choose one only)

a) I have never thought of going outdoors	b) I would consider going outdoors	c) I intend to go outdoors	d) I have started going outdoors	e) I have been going outdoors regularly
☐	☐	☐	☐	☐

13. During the past 2 months, did you expose yourself to sun and/or light: (Please choose one only)

a) Much more than before SCENESSE®	b) More than before SCENESSE®	c) A little more than before SCENESSE®	d) Same as before SCENESSE®	e) Less than before SCENESSE®
☐	☐	☐	☐	☐

NB: This EPP specific questionnaire is part of the proprietary knowledge of Clinuvel and therefore cannot be used without the explicit written permission of Clinuvel.

Patient's Initial/Date: _____ /_____

eTable 1. Description of variables as secondary endpoint

	Definition
Daily activity index (DAI) score	Score based on the questionnaire about daily activity (not validated) and comprises 8 items on a five-point scale. Scores ranges from 0 to 32 points, where a higher score indicates less impairment. -2 answers (does not apply) values were excluded and normalized. Baseline was based on the questionnaire filled in during the first visit (before treatment). The questionnaire was completed during each visit and reflected the past 60 days.
Taking measures score	Score based on the questionnaire about taking measures before going outside (not validated) and comprises 4 items on a five-point scale. Scores range from 0 to 16 points, where a higher score indicates less measures. -2 answers (does not apply) values were excluded and normalized. Baseline was based on the questionnaire filled in during the first visit (before treatment). The questionnaire was completed during each visit and reflected the past 60 days.
Symptoms after light exposure	Score based on the question about symptoms after light exposure (not validated) and comprises 1 item on a five-point scale. Scores ranging from 0 to 4 points, where a higher score indicates less symptoms. Baseline was based on the questionnaire filled in during the first visit (before treatment). The questionnaire was completed during each visit and reflected the past 60 days.
Self-confidence score	Scores based on the questionnaire on how EPP influences life and emotions (not validated) and comprises 7 items on a five-point scale. Scores ranges from 0 to 28 points, where a higher score indicates a better self-confidence. Baseline was based on the questionnaire filled in during the first visit (before treatment). The questionnaire was completed during each visit and reflected the past 60 days.
Influence of EPP on family	Scores based on the question on how EPP has an effect on your family (not validated) and comprises 1 item on a five-point scale. Scores ranges from 0 to 3 points, where a higher score indicates less influence. Baseline was based on the questionnaire filled in during the first visit (before treatment). The questionnaire was completed during each visit and reflected the past 60 days.
Effect of afamelanotide score	Score based on the questionnaire about the effect of afamelanotide (not validated) and comprises 5 items on a five-point scale. Scores ranging from 0 to 20 points, where a higher score indicates less effect of afamelanotide. Baseline was based on the questionnaire filled in during the second visit (after treatment). The questionnaire was completed during each visit and reflected the past 60 days.

eTable 2. Frequency of adverse events for afamelanotide

Adverse event	***n***	***% of total AEs***
Nausea	60	11.4
Fatigue, malaise and tired	51	9.7
Flushing	46	8.8
Nausea and headache	44	8.4
Implant related (e.g. hematoma)	40	7.6
Lack of effectiveness	38	7.2
Headache	37	7.1
Skin, other (e.g. oily skin)	19	3.6
Flu like symptoms	14	2.7
Gastro-intestinal symptoms	13	2.5
Myalgia, paraesthesia's	11	2.1
Dizziness	11	2.1
Allergic reaction, pruritus, itching, redness	10	1.9
Pyrosis	8	1.5
Urogenital tract symptoms	7	1.3
Respiratory tract symptoms	7	1.3
Pigmentation	7	1.3
Nausea, headache and flushes	5	1.0
Transpiration	4	0.8
Pregnancy partner during treatment	3	0.6
None of the above, other	90	17.1

eTable 3. Serious adverse events (SAE) during afamelanotide treatment*

Serious adverse event (description)	Relation to treatment
Transient ischemic attack (TIA), lost control over right arm and leg, recovered after 30 min.	*Not related*
Irresectable glioblastoma, palliative treatment with radiation	*Not related*
Hepatic crisis following excessive alcohol use, treated with erythropheresis and transfusions	*Not related*
Gastro-enteritis and fever in India, short hospitalization for fluid resuscitation	*Not related*
Appendectomy for appendicitis, complicated with peritonitis and abcesses treated with antibiotics	*Not related*
Tibia fracture after a fall	*Not related*
Salmonella enteritis with fever, treated with fluid and potassium resuscitation.	*Not related*
Salmonella infection with fever acquired abroad, hospitalized because of dehydration	*Not related*
Sigmoid resection for diverticulitis (onset: years ago), complicated by a bladder perforation.	*Not related*
Cholecystectomy for symptomatic gallstones	*Not related*
Hospitalization for recurrent intrahepatic biliary obstruction, possibly intrahepatic stones.	*Not related*

** The initially reported SAE erythema of the face 1 hour after implantation, treated with clemastine intravenous was reported for the suspicion of an allergic reaction. Afterwards it seemed to be the adverse event flushes, related to the implant.*

eTable 4. Baseline values (before treatment) for all secondary endpoints

	Median (IQR)
DAI score	16.0 (9.7 – 24.0)
Taking measures score	4.0 (0 – 8)
Symptoms after light exposure	2.0 (1 – 3)
Self-confidence score	17.0 (13 – 23.5)
Influence of EPP on family	2.0 (1 – 2)
Effect of afamelanotide score	5.0 (3.3 – 8)

Abbreviations: n number of patients, DAI daily activity index, EPP erythropoietic protoporphyria, IQR interquartile range.

eTable 5. Mixed models for daily activity index, checking weather score and symptoms question

		95 % CI		
	B	Lower	Upper	**P-value**
Daily Activity Index (DAI) score *				
Treatment effect	6.75	4.99	8.51	**<0.001**
Sex	-0.18	-2.11	1.76	0.86
Age (years)	-0.03	-0.10	0.04	0.41
BMI (kg/m^2)	-0.03	-0.24	0.18	0.78
Month				0.54
January	-0.26	-5.56	5.05	0.92
February	0.25	-3.02	3.52	0.88
March	-0.22	-3.42	2.98	0.89
April	-2.84	-6.94	1.26	0.17
May	-5.18	-10.38	0.02	0.05
June	-6.62	-13.31	0.07	0.05
July	-6.01	-12.96	0.95	0.09
August	-5.21	-11.91	1.48	0.13
September	-5.05	-10.82	0.72	0.09
October	-2.10	-7.09	2.88	0.41
November	-0.96	-5.40	3.49	0.67
December	Reference			
Sunlight score (kJ/cm^2)	0.01	-0.06	0.07	0.78
Time since first treatment (years)	-0.06	-1.10	0.98	0.91
Taking measures score **				
Treatment effect	4.05	3.13	4.96	**<0.001**
Sex	-0.01	-1.26	1.23	0.98
Age (years)	-0.03	-0.08	0.01	0.13
BMI (kg/m^2)	0.10	-0.04	0.23	0.15
Month				**0.01**
January	2.54	-0.25	5.32	0.07
February	2.09	0.38	3.81	**0.02**
March	1.55	-0.13	3.23	0.07
April	1.12	-1.03	3.27	0.31
May	0.01	-2.70	2.73	0.99
June	0.12	-3.39	3.63	0.95
July	1.00	-2.65	4.65	0.59
August	0.56	-2.95	4.07	0.76
September	0.29	-2.73	3.32	0.85
October	1.19	-1.41	3.78	0.37
November	-1.31	-3.66	1.04	0.27
December	Reference			
Sunlight score (kJ/cm^2)	-0.04	-0.07	0.00	**0.04**
Time since first treatment (years)	0.03	-0.53	0.59	0.92
Symptoms after light exposure ***				
Treatment effect	0.59	0.39	0.79	**<0.001**
Sex	0.04	-0.19	0.26	0.74
Age (years)	0.00	0.00	0.01	0.38
BMI (kg/m^2)	0.02	0.00	0.05	0.05
Month				**<0.001**
January	0.64	-0.03	1.32	0.06
February	0.15	-0.26	0.55	0.48
March	0.23	-0.18	0.64	0.27
April	-0.52	-1.01	-0.04	**0.03**
May	-0.54	-1.13	0.06	0.08
June	-0.84	-1.61	-0.07	**0.03**
July	-0.64	-1.44	0.16	0.11
August	-0.62	-1.38	0.15	0.12
September	-0.53	-1.19	0.13	0.12
October	-0.17	-0.74	0.39	0.55
November	-0.28	-0.79	0.23	0.29
December	Reference			
Sunlight score (kJ/cm^2)	0.00	-0.01	0.01	0.93
Time since first treatment (years)	-0.02	-0.14	0.10	0.73

* *Score based on the questionnaire about daily activity.*

** *Score based on the questionnaire about taking measures before going outside.*

*** *Score based on the question about symptoms after light exposure.*

eTable 6. Mixed models for self-confidence score, influence of EPP on family question and effect afamelanotide on EPP

		95 % CI		
	B	Lower	Upper	**P-value**
Self-confidence score *				
Treatment effect	2.41	1.43	3.40	**<0.001**
Sex	-0.02	-1.76	1.73	0.99
Age (years)	0.04	-0.02	0.10	0.19
BMI (kg/m^2)	0.06	-0.12	0.23	0.53
Month				0.06
January	0.26	-3.08	3.59	0.88
February	-0.79	-2.80	1.23	0.44
March	0.29	-1.74	2.33	0.78
April	-2.64	-5.07	-0.20	**0.03**
May	-3.23	-6.24	-0.22	**0.04**
June	-5.02	-8.90	-1.14	**0.01**
July	-4.80	-8.83	-0.78	**0.02**
August	-4.02	-7.89	-0.16	**0.04**
September	-3.26	-6.59	0.08	0.06
October	-1.58	-4.43	1.27	0.28
November	-2.72	-5.27	-0.17	**0.04**
December	Reference			
Sunlight score (kJ/cm^2)	0.00	-0.03	0.04	0.80
Time since first treatment (years)	0.37	-0.27	1.01	0.26
Influence of EPP on family **				
Treatment effect	0.53	0.36	0.70	**<0.001**
Sex	-0.10	-0.32	0.11	0.34
Age (years)	0.00	-0.01	0.00	0.44
BMI (kg/m^2)	0.00	-0.02	0.02	0.89
Month				0.14
January	0.39	-0.19	0.97	0.18
February	0.31	-0.04	0.65	0.08
March	0.43	0.08	0.78	**0.02**
April	0.24	-0.17	0.66	0.26
May	0.29	-0.23	0.80	0.27
June	0.07	-0.59	0.73	0.83
July	0.18	-0.50	0.87	0.60
August	0.07	-0.59	0.73	0.83
September	0.09	-0.48	0.65	0.77
October	0.41	-0.07	0.90	0.10
November	0.12	-0.32	0.56	0.60
December	Reference			
Sunlight score (kJ/cm^2)	0.00	-0.01	0.00	0.19
Time since first treatment (years)	0.02	-0.09	0.13	0.76
Effect of afamelanotide score ***				
Treatment effect	-0.73	-1.68	0.22	0.13
Sex	-0.23	-1.23	0.76	0.64
Age (years)	-0.03	-0.06	0.01	0.12
BMI (kg/m^2)	-0.14	-0.25	-0.03	**0.01**
Month				0.18
January	2.23	-0.63	5.08	0.13
February	1.62	-0.07	3.30	0.06
March	1.96	0.19	3.73	**0.03**
April	1.14	-0.93	3.22	0.28
May	0.41	-2.24	3.05	0.76
June	0.43	-2.97	3.84	0.80
July	0.01	-3.65	3.66	1.00
August	0.39	-3.05	3.82	0.82
September	-0.11	-3.02	2.81	0.94
October	-0.68	-3.15	1.78	0.59
November	0.09	-2.07	2.24	0.94
December	Reference			
Sunlight score (kJ/cm^2)	0.00	-0.04	0.03	0.94
Time since first treatment (years)	-0.03	-0.60	0.54	0.92

* *Scores based on the questionnaire on how EPP influences life and emotions.*

** *Scores based on the question on how EPP has an effect on your family.*
*** *Score based on the questionnaire about the effect of afamelanotide*

eAppendix. PASS protocol

Title	A Post-Authorisation Disease Registry Safety Study to Generate Data on the Long-Term Safety and Clinical Effectiveness of SCENESSE® (Afamelanotide 16mg) in Patients with Erythropoietic Protoporphyria (EPP). [*Short Title:* SCENESSE® PASS-001]
Protocol version identifier	CUV-PASS-001 Version 8
Date of latest version of protocol	7 March 2016
EU PAS register number	Not yet available
Active substance	Afamelanotide Pharmacotherapeutic group: Emollients and protectives, protectives against UV radiation for systemic use ATC code: D02BB02
Medicinal product	SCENESSE® 16 mg
Product reference	Not applicable
Procedure number	EMA/H/C/002548
Marketing authorisation holder	Clinuvel (UK) Limited
Joint PASS	No
Research question and objectives	This non-interventional study has been designed to gather long-term safety data and outcome endpoints. The objectives are to assess whether SCENESSE® can be used safely within designated treatment centres and to generate data to support the clinical effectiveness derived from the use of SCENESSE®
Countries of study	It is anticipated that, in the first year post-MA, distribution will be initiated in the following countries: Austria, Germany, The Netherlands, United Kingdom. Others will be entered into the study as national Competent Authority approvals are obtained.
Authors	Drs Philippe Wolgen and Dennis Wright Level 5/160 Queen St Melbourne, 3000 Australia dennis.wright@clinuvel.com
Marketing authorisation holder	Clinuvel (UK) Limited
MAH contact person	Dr Dennis Wright Level 5/160 Queen St Melbourne, 3000 Australia dennis.wright@clinuvel.com

4. ABSTRACT

Title

A Post-Authorisation Disease Registry Safety Study to Generate Data on the Long-Term Safety and Effectiveness of SCENESSE® (Afamelanotide 16mg) in Patients with Erythropoietic Protoporphyria (EPP). [*Short Title:* SCENESSE® PASS-001]

Rationale and background

In December 2014, marketing authorization for SCENESSE® was granted in Europe under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004). The establishment of a Disease Registry was imposed as a specific obligation with data to be collected from both EPP patients and physicians.

Analyses comparing long term safety data and outcome endpoints in EPP patients receiving treatment with SCENESSE® (Treated Group) and those not receiving SCENESSE® (Untreated Group) or having discontinued treatment with SCENESSE® (Discontinued Group) are to be undertaken.

Research question and objectives

The study has been designed to assess whether SCENESSE® can be used safely within designated treatment centres and to generate data to support the clinical effectiveness of SCENESSE®. The study has the following objectives:

Primary objectives

- Gather long-term safety data of SCENESSE®
- Evaluate compliance with the risk minimization measures

Secondary objective

- Evaluate adherence with the controlled distribution program
- Generate data to contribute to knowledge about clinical benefits and to add data on potential clinical effectiveness of SCENESSE®

Study design

This is a non-interventional post-authorisation study to be conducted in EPP patients eligible for treatment with SCENESSE®. Eligible patients will receive SCENESSE® (afamelanotide 16 mg) on approximate Days 0, 60, 120 and possibly Day 180, if deemed necessary by the treating physician in consultation with the patient, ideally each year. Those participating in the registry study but electing not to receive SCENESSE® will act as controls. In the absence of alternative treatment for EPP, a comparator group consisting of untreated patients

(Untreated Group) will be included. Those who discontinue treatment will be followed up on an annual basis according to the schedule for the Untreated Group

Safety assessment will occur throughout the study. Treatment-emergent adverse events and the use of concomitant medications will be assessed at every visit to the treatment centre. Compliance with the risk minimization measures will be assessed throughout the study while the effectiveness of the controlled distribution of SCENESSE® will be evaluated every 12 months.

Clinical effectiveness of SCENESSE® will be assessed at regular intervals during the study by evaluating:

- Longitudinal assessment of those remaining on treatment and the reasons for discontinuing (and recommencing) treatment
- Longitudinal assessment of behaviours and activities able to be undertaken using a Daily Activity Inventory
- Quality of life assessment (EPP-QoL)
- Sun protection measures used and number and severity of phototoxic reactions experienced.

Setting

It is the intention of the MAH to supply SCENESSE® only to patients (via EPP Expert Centres) who are eligible for treatment per SmPC and who are registered on the European EPP Disease Registry database. It is further proposed that the European EPP Disease Registry will be available at all treatment centres.

Population

Adult patients with erythropoietic protoporphyria (EPP): eligibility for treatment will be based on a positive diagnosis for EPP and the lack of any contraindications for treatment with SCENESSE®, as described in the approved SmPC. Both treated and untreated patients will be enrolled in the study.

Variables

Safety variables:

Characterisation of the overall long-term safety profile with regard to all adverse events will be undertaken. Treatment-emergent adverse events will be summarized by MedDRA preferred term and body system, and these will be further summarized by intensity, seriousness and relationship to study medication. In addition to assessing the overall adverse event profile, there will be a particular emphasis on:

- Use during pregnancy and lactation

- changes in cutaneous efflorescence and pigmentary expressions
- application site reactions
- hypersensitivity and allergy

Clinical effectiveness variables:

The clinical effectiveness of treatment with SCENESSE® will be evaluated by a number of tools/questionnaires which will measure/record any changes to:

- Longitudinal assessment of those remaining on treatment
- Quality of Life (EPP-QoL)
- Daily Activity Inventory
- Sun protection measures and phototoxicity (number and severity of events)

Risk minimisation measures:

Compliance with risk minimization recommendations will be measured through the Disease Registry for the following:

- off-label use in adults and paediatric patients
- use in pregnancy and lactation
- administration errors
- changes in cutaneous efflorescence and pigmentary expressions
- application site reactions.

Controlled distribution measures:

Full drug accountability records from institutional pharmacy records and physicians' SCENESSE® administration documentation will be captured through the registry.

Data sources

The European EPP Disease Registry will have data entered by the Institutional staff as per the data contained in the patients'/ centre's source documents. These data will be entered into electronic CRFs in pseudonymised form.

Data for the analyses will be extracted from the European EPP Disease Registry database by the CRO responsible for data management.

These data will be captured in the registry and drug exposure will be determined by the number of administrations as recorded on the electronic CRFs.

Study size

EPP is an ultra-orphan indication (estimated to affect less than 1 in 50,000 individuals), therefore patient numbers in the study will be limited. It is anticipated that in the first two

years the study will enrol 200 patients from an estimated eligible population of 660 patients with EPP. It is likely that at most 10% of these will not receive SCENESSE® treatment. The study will run indefinitely.

Data analysis

Sample Size Calculation for Safety Data

On the basis of 200 patients treated with SCENESSE® there will be a:

- >99% chance of observing at least one adverse event of a specific type if the true incidence of that specific adverse event is common (10%)
- 87% chance of observing at least one adverse event of a specific type if the true incidence of that specific adverse event is uncommon (1%)
- 18% chance of observing at least one adverse event of a specific type if the true incidence of that specific adverse event is rare (0.1%)

Safety Assessment

All patients enrolled in the registry will be included in the safety assessment. In general longitudinal comparisons will be within Treated Groups (including separate groups that take into account patients who commence or discontinue treatment) and between groups, Treated versus Untreated.

The number of participants with treatment-emergent adverse events will be summarized by MedDRA PT and body system. Adverse events will be further summarized by intensity, seriousness and outcome. Adverse events will also be summarized by 6 monthly time intervals from entry into the registry to assess the longitudinal effect of the treatment and EPP. There will be a particular emphasis on the following types of adverse events:

Changes in cutaneous efflorescence – a dermatological examination once every six months (equating roughly to the end of treatment in Year 1 and then prior to and at the end of the treatment period in subsequent treatment years) with an emphasis on pre-existing expressions, new cutaneous efflorescence and pigmentary expressions and/or sun damaged fields will be conducted by a dermatologist. Full body photography will be undertaken at the same time. Documentation of full body skin examination will be performed as per current clinical practice. Any changes in cutaneous efflorescence and pigmentary expressions deemed to require treatment will be treated appropriately and severity, causality and outcome will be assessed by the treating physician and/or dermatologist.

Application site reactions – these will be reported following each SCENESSE® administration. Severity, causality and outcome will be assessed by the treating physician. The incidence of application site reactions will be determined by comparing the number of

reports with the number of SCENESSE® administrations. The acceptability criterion is that such reactions occur in less than 25% of administrations.

Allergy and hypersensitivity - these will be reported following each administration. Severity, causality and outcome will be assessed by the treating physician. The incidence of reactions requiring hospitalisation will be determined. Acceptability criterion is less than 10% of reactions that require hospitalisation.

Off-label use (in children or adults without EPP) – demographic data and confirmation of EPP diagnosis will be recorded at baseline. The incidence of treated patients who do not comply with the requirements of the SmPC for age or disease status will be determined. Acceptability criteria are:

- off-label use in children represents not more than 1% of all cases
- use in adults who do not have EPP is not more than 5% of all cases

Use in pregnancy or lactation – reports of use during pregnancy or lactation will be collected and followed up and the acceptability criterion is less than 5% of women treated with SCENESSE® become pregnant or breastfeed during treatment.

Administration errors – these will be recorded and the acceptability criterion is that administration errors occur in no more than 5% all prescriptions.

Assessment of Clinical Effectiveness

Continuity on treatment - together with logs detailing reasons for discontinuing (and those recommencing)

Quality of Life (EPP-QoL) – will be measured using the EPP-QoL questionnaire, provided to the patient for completion at baseline prior to treatment in Year 1 and at each subsequent visit.

Daily Activity Inventory – will be evaluated using the questionnaire provided to the patient for completion at baseline prior to treatment in Year 1 and at each subsequent visit. In addition, patients' statements on their experience with SCENESSE® will be recorded at the end of each treatment year.

Light and Sun Protection Measures – patients will be asked to report the sun protection measures employed.

Phototoxicity – patients will be asked to report the number and severity of phototoxic reactions and episodes experienced.

Risk minimisation measures:

Changes in cutaneous efflorescence – compliance with 6 monthly full body examinations.

Application site reactions – compliance with the provision of educational material, and the training and accreditation of all physicians who will administer SCENESSE®. The acceptability criterion for reactions is less than 25% of administrations.

Off-label use (in children or adults without EPP) – demographic data and confirmation of EPP will be recorded at baseline. The incidence of treated patients who do not comply with the requirements of the SmPC for age or disease status will be determined. Acceptability criteria are:

- off-label use in children represents not more than 1% of all cases
- use in adults who do not have EPP is not more than 5% of all cases

Use in pregnancy or lactation – acceptability criterion is less than 5% of women treated with SCENESSE® become pregnant or breastfeed during treatment.

Administration errors – The acceptability criterion is that administration errors occur in no more than 5% all prescriptions.

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1 (Original)	04 March 2015	N/A	N/A	N/A
2	24 June 2015	N/A Protocol not yet approved	N/A Protocol not yet approved	PRAC assessment report (12 May 2015)
3	20 August 2015	N/A Protocol not yet approved	N/A Protocol not yet approved	PRAC assessment report (14 August 2015)
4	28 August 2015	N/A Protocol not yet approved	N/A Protocol not yet approved	Preliminary PRAC assessment report (28 August 2015)
5	8 September 2015	N/A Protocol not yet approved	N/A Protocol not yet approved	Preliminary PRAC assessment report (8 September 2015)
6	8 December 2015	N/A Full protocol not yet approved	N/A Full protocol not yet approved	Protocol amendments in line with commitments given following September 2015 PRAC Meeting
7	17 February 2016	N/A Full protocol not yet approved	N/A Full protocol not yet approved	Preliminary PRAC assessment report (9 February 2016)
8	07 Mar 2016	N/A Full protocol not yet approved	N/A Full protocol not yet approved	PRAC List of Outstanding Issues (04 Mar 2016)

7. RATIONALE AND BACKGROUND

Erythropoietic protoporphyria (EPP) is an orphan indication and since there are no medicinal products in the Community available for the therapeutic indication, there is currently a clear unmet medical need for treatment.

In December 2014, marketing authorization for SCENESSE® was granted in Europe under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004). Following are the reasons why comprehensive data on the efficacy and safety of SCENESSE® under normal conditions of use could not be provided:

- EPP is an extremely rare condition and there are not sufficient naïve patients available that are able and willing to join a clinical trial;
- it would be medically unethical to collect such efficacy data owing to the fact that EPP patients are unwilling to expose themselves to light sources or sunlight based on past preconditioning from ingrained anxiety of burning;
- there is no existing satisfactory assessment tool to capture meaningful and comprehensive efficacy data for afamelanotide.

Currently, the most relevant safety concern is the lack of long-term safety data which are considered essential because SCENESSE® is intended as a life-long therapy. To address this, the establishment of a Disease Registry was imposed as a specific obligation with data to be collected from both patients and physicians. Outcome endpoints to provide an indication of effectiveness were also to be collected.

The CHMP also requested a retrospective chart review study be undertaken. Analyses comparing long term safety data and outcome endpoints in patients receiving treatment with SCENESSE® (Treated Group) and those not receiving SCENESSE® (Untreated Group) or having discontinued treatment (Discontinued Group) with SCENESSE® to be undertaken.

Another objective of the study should be the assessment of the compliance with risk minimization recommendations and the controlled access program for patients receiving SCENESSE®.

The CHMP concluded that a positive benefit/risk balance for SCENESSE® had been established and recommended the granting of a marketing authorisation under exceptional circumstances subject to the obligations stated above.

8. RESEARCH QUESTION AND OBJECTIVES

The study has been designed to assess whether SCENESSE® can be used safely within porphyria treatment centres and to generate data on long term safety and outcome endpoints derived from the use of SCENESSE®. The recommended risk minimization measures and the effectiveness of the controlled distribution of SCENESSE® will also be assessed. The objectives are as follows:

Primary objectives

- Gather long-term safety data on SCENESSE® with respect to:
  - Characterisation of the long-term safety profile with regard to all adverse events
  - Changes in cutaneous efflorescence and pigmentary expressions (type, incidence and severity, and determine if there is a change of incidence or the emergence of new adverse events following repeated administration, including occurrence of skin cancer or precursors)
  - Application site reactions (type, incidence and severity, and determine if there is a change of incidence or the emergence of new adverse events following repeated administration)
  - Allergy and hypersensitivity (type, incidence and severity, and determine if there is a change of incidence or the emergence of new adverse events following repeated administration)
  - Administration errors (identify if any errors occur and if there are any associated adverse events).

- Evaluate compliance with the risk minimization measures:
  - Cutaneous efflorescence and pigmentary expressions - compliance with 6 monthly full body examinations
  - Application site reactions – compliance with the provision of educational material, and the training and accreditation of all physicians who will administer SCENESSE®
  - Off-label use - undertake routine assessments of database to determine the number of cases of use in children or adults without EPP
  - Use in pregnancy or lactation – undertake routine assessments of database to determine the number of cases of use during pregnancy or lactation
  - Administration error - compliance with the provision of educational material, and the training and accreditation of all physicians who will administer SCENESSE

Secondary objective

- Evaluate adherence to the controlled distribution program:

- This will be done through drug accountability records with quantities of SCENESSE® shipped to treatment centres compared with records of administered SCENESSE® and institutional pharmacy stocks (a “mass balance” will be determined)
- Given the limited number of patients likely to be recruited per treatment centre, distribution to institutional pharmacies will be done using small shipments. Records of SCENESSE® shipped will be available for individual batches and the batch number of each SCENESSE® administered will be recorded on the patient’s CRF. Regular reports of shipments and SCENESSE® administered by patient number and by batch will be generated from the database. These data will be used to produce full accountability reports.

- Generate <u>data to contribute to knowledge about clinical benefits and to add data on potential clinical effectiveness of SCENESSE®</u>
  - Longitudinal assessment of activities able to be undertaken prior to treatment and those possible following commencement of treatment (using the Daily Activity Inventory)
  - Longitudinal assessment of those remaining on treatment together with logs detailing reasons for discontinuing (and those recommencing) treatment as well as those declining treatment will be done using descriptive statistics. Reasons for declining treatment, discontinuing treatment and recommencing treatment will be categorised and frequency tables generated
  - Quality of Life assessment using EPP-QoL questionnaire
  - Sun protection measures employed and number and severity of phototoxic reactions experienced

9. RESEARCH METHODS

9.1. Study design

This is a non-interventional post-authorisation registry study. All eligible patients who have a confirmed diagnosis of EPP and who provide written consent to have their data entered into the European EPP Disease Registry database will be enrolled in the study, that is consented treated and untreated patients. Further to eligibility confirmation, as per the SCENESSE® SmPC, patients may elect to receive SCENESSE® or not to be treated. It is the intention of the MAH not to treat any EPP patients who have not consented to participation in the European EPP Disease Registry.

Screening logs will be used to record information on all patients contacted by treatment centres. Patients who indicate their willingness to participate and who are consented will have their data recorded on the disease registry CRF, while the reasons given by those who do not wish to participate will be recorded on the screening logs. “Baseline” data collected on screening logs will allow for a comparison of the characteristics of patients agreeing to participation with those of patients who decline to participate.

Eligible patients who choose to be treated will receive SCENESSE® on approximate Days 0, 60, 120 and possibly Day 180, if deemed necessary by the treating physician, ideally each year. In the absence of alternative treatment for EPP, a comparator group consisting of untreated patients (Untreated Group) will be included in the study. Those who discontinue treatment will be followed up on an annual basis according to the schedule for the Untreated Group. The study will continue indefinitely.

Safety assessment as outlined above will occur via the European EPP Disease Registry. Treatment-emergent adverse events and the use of concomitant medications will be assessed at every visit to the treatment centre and recorded using electronic CRFs. Compliance with the risk minimization measures will be assessed against the designated criteria throughout the study while the effectiveness of the controlled distribution of SCENESSE® will be evaluated every 12 months.

Clinical effectiveness of SCENESSE® will be assessed at regular intervals by evaluating:

- Longitudinal assessment of those remaining on treatment and the reasons for discontinuing (or recommencing) treatment
- Longitudinal assessment of activities able to be undertaken using the Daily Activity Inventory
- Quality of Life assessment using the EPP-QoL questionnaire
- Sun protection measures used and the number and severity of phototoxic reactions experienced.

Results from patients treated with SCENESSE® (Treated Group) will be compared with those of patients who are not treated (Untreated Group) or who discontinue treatment (Discontinued Group) with SCENESSE®.

9.2. Setting

It is the intention of the MAH to supply SCENESSE® only to patients (via porphyria treatment centres) who are eligible for treatment in accordance with the SmPC and who have agreed to being registered on the European EPP Disease Registry. It is further proposed that the European EPP Disease Registry be available at all treatment centres. For details of the registry please refer to the separate document entitles "Electronic European EPP Disease Registry".

Eligibility Criteria for Treatment

To be eligible for treatment, patients must meet the following criteria:

- Patients with erythropoietic protoporphyria (EPP)
- Aged 18 years or more
- Patient where treatment is not contraindicated in accordance with the approved SmPC.

Non-eligibility Criteria for Treatment

If the following SCENESSE® contraindications apply, the patient is not eligible for treatment, but can still be enrolled in the untreated 'comparator' group:

- Allergy or hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of SmPC
- Presence or history of severe hepatic disease
- Hepatic impairment
- Renal impairment
- Children and adolescents (0-17 years)

Women of childbearing potential should use effective contraception during treatment with SCENESSE® and for a period of three months thereafter. SCENESSE® should not be used during pregnancy.

It is unknown whether afamelanotide or any of its metabolites are excreted in breast milk, so SCENESSE® should be avoided during breastfeeding.

Additionally, a careful clinical decision must be made whether to treat patients with any clinically significant disorders of the gastrointestinal, cardiovascular, respiratory, endocrine (including diabetes, Cushing's disease, Addison's disease, Peutz-Jeghers syndrome), neurological (including seizures) and haematological (especially anaemia) systems. If such

patients are treated they must be monitored closely after each administration, including vital signs, haematology and biochemistry.

SCENESSE® should not be used in patients over 70 years of age. If such patients are treated, they must be monitored after each administration, including vital signs, routine haematology and biochemistry.

Full a matrix of all study procedures, please refer to Appendix G.

9.3. Variables

Safety variables:

Treatment-emergent adverse reactions, coded as MedDRA PTs, will be closely monitored with particular emphasis on:

Characterisation of the long-term safety profile with regard to all adverse events

The MedDRA adverse event dictionary will be used to map verbatim adverse event terms to preferred terms and body systems. Intensity, seriousness and relationship to study medication will be recorded.

The number of participants who terminate treatment early due to adverse events related to study medication will be tabulated.

Pregnancy and Lactation

If reports of use during pregnancy or while breastfeeding are received, details will be recorded and appropriate follow up will be initiated and undertaken to provide data on clinical outcomes.

Changes in cutaneous efflorescence and pigmentary expressions

MedDRA terms to be assessed are listed in Appendix B. These terms will be grouped according to appropriate MedDRA High Level Terms or High Level Group Terms (as appropriate).

Application site reactions

MedDRA terms to be assessed are listed in Appendix C. These terms will be grouped according to appropriate MedDRA High Level Terms or High Level Group Terms (as appropriate). The incidence of application site reactions will be determined by comparing the number of reports with the number of SCENESSE® administrations. Acceptability criterion is less than 25% of application site reactions, whereby normally expected injection site micro trauma will be taken into account.

Hypersensitivity and allergy

The following terms related to allergies and hypersensitivity will be used for post-marketing surveillance:

- Hypersensitivity Standard MedDRA Query broad and narrow

No allergic or hypersensitivity reactions possibly, probably or definitely related to afamelanotide have been reported to date in any patient population treated in a clinical trial. Studies on hospital-based inpatient populations have shown a prevalence of allergic reactions ranging from 0.18% to 0.42%. An incidence greater than this in SCENESSE®-treated patients or a change in seriousness (non-serious to serious) will trigger a reassessment of the existing risk minimisation measures.

Clinical effectiveness variables:

The clinical effectiveness of treatment with SCENESSE® will be evaluated by a number of tools/questionnaires which will measure/record any changes to:

Longitudinal assessment of those remaining on treatment

Regular assessment of the number of patients who remain "compliant" with the treatment schedule will be undertaken as will be an assessment of the reasons given for discontinuation of treatment (and restarting treatment, if appropriate).

Quality of life (EPP-QoL)

Quality of life will be assessed at baseline prior to treatment in Year 1 and at each subsequent visit. The EPP-QoL questionnaire (see Appendix D), which is currently being validated, will be used for this assessment and provided to the patient for completion. There is no other QoL assessment tool that is capable of assessing the impact of visible light exposure on the quality of life of an EPP patient, including the DLQI.

Daily Activity Inventory

An inventory of behaviours and activities capable of being undertaken by the EPP patient will be assessed through the completion of the Daily Activity Inventory (see Appendix E) provided at baseline prior to treatment in Year 1 and at each subsequent visit.

Sun protection measures and phototoxicity

At each visit the patient will be asked direct questions by the treating physician about the light and sun protection measures he or she uses to protect him or herself from light/the sun and the number and severity of phototoxicity experienced. The physician will record all answers.

These will also be captured in the Daily Activity Inventory.

Risk minimisation measures:

Compliance with risk minimization recommendations will be measured through the Disease Registry to ensure that the following do not occur:

Off-label use in adult and paediatric patients

The incidence of treated patients who do not comply with the requirements of the SmPC for age or disease status will be determined. Acceptability criteria are:

- off-label use in children represents not more than 1% of all cases
- use in adults who do not have EPP is not more than 5% of all cases

Use in pregnancy and lactation

Acceptability criterion is less than 5% of women treated with SCENESSE® become pregnant or breastfeed during treatment

Administration errors

The acceptability criterion is that administration errors occur in no more than 5% all administrations.

In addition, compliance with the measures to minimise risk, the risk associated with the following will be assessed:

Cutaneous efflorescence and pigmentary expressions - compliance with 6 monthly full body examinations

Application site reactions – compliance with the provision of educational material, and the training and accreditation of all physicians who will administer SCENESSE®. The acceptability criterion for application site reactions is less than 25% of administrations.

Controlled distribution measures:

The objective is the assessment of the compliance with the controlled access program for patients receiving SCENESSE®. The number of drug product unit doses distributed to designated treatment centres' pharmacies will be available from distribution records of the CRO responsible for product distribution. SCENESSE® usage by each treatment centre will be available from the European EPP Disease Registry, because treating physicians will be required to identify and record the SCENESSE® batch administered on an electronic CRF following each administration.

Drug product unit doses distributed to centres will be reconciled with the number administered and the number remaining in the institutional pharmacies. The "mass balance" will determine the level of compliance. The number of unaccounted drug product unit doses

will be divided by the total number of SCENESSE® doses received by the institutional pharmacy to determine the level of non-compliance on a percentage basis.

9.4. Data sources

The European EPP Disease Registry will have data entered by the institutional staff as per the data contained in the patients'/centre's source documents. These data will be entered into electronic CRFs. Separately, details are provided on the European EPP Disease Registry which outline details on data ownership, data collection and entry into the database. (See "Electronic European EPP Disease Registry" document for more details of the registry.) All treatment centres will participate in the European EPP Disease Registry.

The source documents containing the data include the following, but not limited to: physicians' and staff progress notes, prescriptions, medical records, laboratory and imagery reports, photographs, quality of life measures, evaluation of daily activities undertaken, sun protection measures used, phototoxicity experienced, and pharmacy stock records. Records, CRFs relating to cutaneous efflorescence and pigmentary expressions will be kept and entered by qualified and appropriately trained personnel, and preferably by a dermatologist.

Data for the analyses will be extracted from the European EPP Disease Registry database by the CRO responsible for data management.

Concerning patient exposure to SCENESSE®, the controlled distribution of SCENESSE® will require the physician and institutional pharmacist to record all prescriptions, dispensing and administrations per EPP patient such that exposure should be able to be easily determined to the individual patient administration level. These data will be captured in the registry and exposure will be determined by the number of administrations as recorded on the electronic CRF pages. All data sources will be similar to those used during the clinical trials.

9.5. Study size

EPP is an orphan indication (estimated to affect less than 1 in 50,000 individuals), therefore patient numbers in the study will be limited. It is anticipated that the study will enrol 200 patients in the first two years from an estimated European total of 660 in the national databases (see Appendix F). The estimate for patients participating in the European EPP Disease Registry study but electing not to be treated with SCENESSE® is expected be at most 10% of these numbers. That is, 20 patients.

All patients who provide written consent to have their data entered into the European EPP Disease Registry database will be enrolled in the study. Further to eligibility confirmation, as per SmPC, they may elect to receive SCENESSE® or not to be treated. EPP patients who consent to having their data recorded on the Disease Registry database but who do not wish

will be divided by the total number of SCENESSE® doses received by the institutional pharmacy to determine the level of non-compliance on a percentage basis.

9.4. Data sources

The European EPP Disease Registry will have data entered by the institutional staff as per the data contained in the patients'/centre's source documents. These data will be entered into electronic CRFs. Separately, details are provided on the European EPP Disease Registry which outline details on data ownership, data collection and entry into the database. (See "Electronic European EPP Disease Registry" document for more details of the registry.) All treatment centres will participate in the European EPP Disease Registry.

The source documents containing the data include the following, but not limited to: physicians' and staff progress notes, prescriptions, medical records, laboratory and imagery reports, photographs, quality of life measures, evaluation of daily activities undertaken, sun protection measures used, phototoxicity experienced, and pharmacy stock records. Records, CRFs relating to cutaneous efflorescence and pigmentary expressions will be kept and entered by qualified and appropriately trained personnel, and preferably by a dermatologist.

Data for the analyses will be extracted from the European EPP Disease Registry database by the CRO responsible for data management.

Concerning patient exposure to SCENESSE®, the controlled distribution of SCENESSE® will require the physician and institutional pharmacist to record all prescriptions, dispensing and administrations per EPP patient such that exposure should be able to be easily determined to the individual patient administration level. These data will be captured in the registry and exposure will be determined by the number of administrations as recorded on the electronic CRF pages.

All data sources will be similar to those used during the clinical trials.

9.5. Study size

EPP is an orphan indication (estimated to affect less than 1 in 50,000 individuals), therefore patient numbers in the study will be limited. It is anticipated that the study will enrol 200 patients in the first two years from an estimated European total of 660 in the national databases (see Appendix F). The estimate for patients participating in the European EPP Disease Registry study but electing not to be treated with SCENESSE® is expected be at most 10% of these numbers. That is, 20 patients.

All patients who provide written consent to have their data entered into the European EPP Disease Registry database will be enrolled in the study. Further to eligibility confirmation, as per SmPC, they may elect to receive SCENESSE® or not to be treated. EPP patients who consent to having their data recorded on the Disease Registry database but who do not wish

to receive treatment or who do not meet the eligibility criteria for treatment will be enrolled as controls.

Since EPP patients have never had access to an effective treatment, the majority of patients only report to the expert centres for a hepatic check-up, recommended by gastroenterologists to be performed annually. Patients have proven motivation to receive treatment but have been up to recently non-adherent to protocols written by expert centres to present their hepatic status. With access to an effective treatment it is expected that EPP patients will prove much more treatment adherent to attend the treatment centres, as seen from the adherence from 2010 to 2015 in Italy and Switzerland.

9.6. Data management

The medical data of all patients treated (Treated Group) with SCENESSE® will be recorded by staff at EPP expert centres as pseudonymised data, with special emphasis on long-term safety and use of the drug captured through logs and the disease registry. Centres will also be requested to upload psuedonymised data of EPP patients who do not receive treatment (Untreated Group) and/ or have discontinued treatment (Discontinued Group) with SCENESSE®.

The MAH is using a bespoke, European EPP Disease Registry in collaboration with Erasmus Medical Centre (EMC) in Rotterdam, following feedback from clinical experts treating EPP patients.

All data will be recorded in individual source documents which will be retained by the treating physician's institution and only psuedonymised data will be entered into electronic CRF pages which have been purpose-designed for the required data capture. All electronic CRF information will be entered by institutional staff. Records, CRFs relating to cutaneous efflorescence and pigmentary expressions will be kept and entered by qualified and appropriately trained personnel, and preferably by a dermatologist.

A study monitor will perform source data verification of data entered into the electronic CRF, and raise queries for correction by the site, if necessary. The data entered into the electronic CRF will be subject to data validation checks for consistency and completeness by the data management CRO. Data queries will then be generated and sent to the treatment centres for clarification/amendment before the database is locked, and released for statistical analysis.

Full Details of the disease registry are provide in the document titled "Electronic European EPP Disease Registry".

9.7. Data analysis

Statistical Analysis Plan

A statistical analysis plan (SAP) will be formalised to describe the statistical methods in greater detail. The SAP will be finalised prior to the first intermediate report, taking into account the treatment choices of those patients who enter the Registry and the resulting pattern of data recorded. At this time, those data are not known. Given the non-interventional nature of the study and the freedom of patients to choose a preventative treatment option that is appropriate to their needs for the first time, only after early experience with recruitment and treatment there will be some certainty about treatment groups for data analysis. As a consequence, the SAP will be reviewed prior to each intermediate report, and modified if the pattern of data recorded has changed in a material way.

Table and listing shells have been developed alongside this Study Protocol, and are consistent with the detailed planned statistical methods and plan contained within this Study Protocol. Below are the proposed treatment groups and planned methods for data analysis.

Treatment Groups

Two treatment groupings (A and B) will be used to summarise the data recorded in the Registry. Treatment grouping A simply distinguishes those that receive SCENESSE during the Registry study from those who do not. Treatment grouping B distinguishes those patients who start or stop SCENESSE® during the trial based on the initial decision to receive SCENESSE or not on entry to the Registry. For each set of endpoints, the treatment grouping will be clearly distinguished. Some patients may swap treatment groups within a treatment grouping during the Registry. If a patient does stop treatment but remains on the registry then data will be collected annually.

Treatment Groups (A)	
A I	Treated with at least one dose of SCENESSE on Registry
A II	Untreated with SCENESSE on Registry

Treatment Groups (B)		
B I	Treated with SCENESSE on Registry, ongoing	
B II	Untreated with SCENESSE on Registry, ongoing	
B III	Treated with SCENESSE on Registry	Stopped SCENESSE, remained on Registry
B IV	Did not receive SCENESSE on entry to Registry	Started SCENESSE during the Registry

Treatment grouping AI, may also be split further into Continuous SCENESSE use (AIc) versus Non-continuous SCENESSE use (AInc). This grouping will be used to distinguish those patients who take SCENESSE regularly during each calendar year (3-4 doses) from those that take SCENESSE less regularly (<3 doses per calendar year), but remain on treatment in the registry.

The grouping will be used in later reporting years if the A and B treatment groupings are not able to capture the long-term treatment patterns adequately.

In addition, patients will be assigned to one of three subgroups based on their SCENESSE exposure at entry into the registry.

Subgroup			
SCENESSE® Status on entry to Registry	Off-treatment, but previously received SCENESSE	On-treatment SCENESSE	Naïve

EPP is a seasonal disease with the severity of phototoxicity worse in Spring and Summer. For this reason EPP patients will ideally receive treatment at the following times; early-Spring (equating to Day 0), late-Spring (equating to Day 60), mid-Summer (equating to Day 120) and early-Autumn (equating to Day 180). In order to take seasonality into account in the proposed summaries, patients will be assigned to one of six subgroups based on their Season of Enrolment. Depending on the actual pattern of enrolment, subgroups may be combined.

Subgroup						
Season of Enrolment	January - February	March - April	May - June	July-August	September - October	November - December

Missing data

There will be no imputation for data that are not recorded at a visit or where a visit did not occur. Since this is a non-interventional study, patients will exhibit distinct visit patterns and in general the exposure avoidance behaviour exhibited by EPP patients is distinct. Furthermore due to the seasonal influence on EPP, carrying data forward is inappropriate. Instead a visit window approach as detailed below will be used to map and summarise the data recorded for treated and untreated patients.

Visit Windows

Treated patients will follow a different visit schedule to untreated patients. Furthermore treated patients may enter the Registry during different seasons of the year such that a full cycle of treatment (Days 0, 60, 120 with 180 option) may not occur during year 1. Untreated patients are asked to attend a treatment centre annually only and may also enter the Registry during different seasons. A visit window approach will be used to map and summarise the clinical effectiveness data recorded throughout the duration of the Registry. Different visit windows will be used for the within treatment group summaries and for the between group (treated versus untreated patients) summaries

Visit Window I (VWI). For the treated group only, including those patients who initially do not receive treatment, the following 60-day post-baseline windows will be used (29-90 days; 91-150 days; 151-210 days; 211-270 days; 271-330 days; 331-393 days) for year 1, and similarly for year "n" such that (n-1) x 365 days is added to each window (e.g. 394-455 days, etc.). For those patients in treatment group BIV, baseline will be the last untreated visit and the visit windows will apply from the date of first treatment. If there is more than one visit in each window, then the latest visit will be used.

Visit Window II (VWII). Comparisons between untreated and treated patients will be undertaken annually whereby a window of 365 days ± 30 days will be used for year 1 and (365 days x n) ± 30 days for the n^{th} year more generally. If there is more than one visit in this window, then the latest visit will be used. (For sun protection measures and phototoxic reaction review, evaluations will also be undertaken for untreated patients on day 180 of each annual cycle. For these variables an additional window will be added for year 1 at 180 days ± 30 days and at (180 days x n) ± 30 days for the n^{th} year thereafter.)

Risk Factors and Potential Confounders

The following additional risk factors for EPP patients have been identified:

- History of skin cancer (Risk of skin cancer)
- Fitzpatrick skin type (Risk of skin cancer)
- Family history of melanoma (Risk of skin cancer)
- History of asthma (Risk of allergy or hypersensitivity reactions)
- History of allergies (Risk of allergy or hypersensitivity reactions)

A number of potential baseline confounding factors have been identified:

- SCENESSE exposure at entry
- Season of enrolment
- Seasonality of treatment
- Gender
- Age
- Baseline severity of disease
- Anxiety
- Depression
- Country/Treatment Centre
- Employment Status

Where appropriate, safety and clinical effectiveness data will be summarised by the risk factors and potential confounding factors. A presentation of the results of stratified analyses per subgroups with and without risk factors and confounders will be provided in the interim and final reports.

Safety Assessment

Sample Size Calculation for Safety Data

On the basis of 200 patients treated with SCENESSE® there will be a:

- >99% chance of observing at least one adverse event of a specific type if the true incidence of that specific adverse event is common (10%)
- 87% chance of observing at least one adverse event of a specific type if the true incidence of that specific adverse event is uncommon (1%)
- 18% chance of observing at least one adverse event of a specific type if the true incidence of that specific adverse event is rare (0.1%)

Analysis of Safety

All patients enrolled in the registry will be included in the safety assessment.

Adverse events

The number of participants with treatment-emergent adverse events will be summarized by MedDRA PT and body system. For those patients who do not receive SCENESSE, treatment-emergent will be defined as adverse events that start on or after the day of entry to the registry. Adverse events will be further summarized by intensity, seriousness and outcome. Adverse events will also be summarized by 6 monthly time intervals from entry into the registry to assess the longitudinal effect of treatment and EPP. New and ongoing adverse events will be captured within specific time periods (period prevalence approach). The denominator for each time period will include all patients remaining in the registry in that period.

Treatment Grouping A will be used for overall incidence of new or worsening TEAEs recorded from the day of entering the Registry (AI versus AII).

Overall incidence of TEAEs will also be summarised by Treatment Grouping B to compare TEAEs on treatment with those off-treatment. Note that patients can appear in both groups in this summary:

(BI + BIII [up until 2m after last dose] + BIV [from time of first dose]) versus

(BII + BIII [from 2m after last dose of SCENESSE] + BIV [up until time of first SCENESSE dose])

Treatment Group AI will be used for TEAEs associated with implant (e.g. implant site reaction), with treatment emergent defined as a new or worsening AE within two months of implant date. In this case the denominator will be the number of implants.

Treatment Grouping B will be used for TEAE period prevalence (new or ongoing AEs in 6 month intervals from registry entry date). TEAEs will be summarised by groups (BI + BIII [up until 2m after last dose]) versus (BII + BIV [up until time of first SCENESSE dose]

The TEAEs will also be summarised by treatment grouping within each "SCENESSE exposure at entry" subgroup, where appropriate.

SAEs will be summarised in an identical way to TEAEs.

There will be a particular emphasis on the following types of adverse events:

Changes in cutaneous efflorescence and/or pigmentary expressions – a dermatological examination and full body photography will be undertaken at baseline by a dermatologist. Any suspect pre-existing lesions and/or sun damaged fields will be identified, photographed and their distribution recorded. If needed, further diagnostics on the lesions/ efflorescence will be performed prior to treatment. Once every six months thereafter (equating roughly to the end of treatment in Year 1 and then prior to and at the end of the treatment period in subsequent treatment years) a dermatological examination with an emphasis on pre-existing lesions and/or sun damaged fields will be conducted. Full body photography will be performed at the same time. Any changes in cutaneous efflorescence and pigmentary expressions will be treated appropriately and severity, causality and outcome will be assessed by the treating physician and/or dermatologist. Records, CRFs relating to cutaneous efflorescence and pigmentary expressions will be kept and entered by qualified and appropriately trained personnel, and preferably by a dermatologist.

Dermatological examination data will be summarised at baseline and by visit, where data are available. The number and percentage of positive cutaneous efflorescence and/or pigmentary expressions will be summarised and whether there are any new expressions since the last visit. The percentage of patients with at least one change post-baseline will be summarised by treatment grouping A. Oral cavity examination will be summarised in the same way. That is, the number and percentage of oropharyngeal epithelium pigmentary expressions for each of oropharynx, buccal mucosa, floor of mouth, tongue epithelium, gingiva, salivary glands, and whether there are any new expressions since the last visit. All data will be listed, including comments recorded. Documentation of full body skin examination will be performed as per current clinical practice.

The data will also be summarised by "SCENESSE exposure at entry" (3 subgroups), Fitzpatrick skin type (6 subgroups, I-VI), Current skin cancer [Yes/No], History of skin cancer [Yes/No], Family history of Melanoma [Yes/No]

Application site reactions – these will be reported following each administration. Severity, causality and outcome will be assessed by the treating physician. The incidence of application site reactions will be determined by comparing the number of reports with the number of

drug products administered. Acceptability criterion is that such reactions are reported in less than 25% of administrations.

Allergy and hypersensitivity - these will be reported following each administration. Severity, causality and outcome will be assessed by the treating physician. The incidence of reactions requiring hospitalisation will be determined. Acceptability criterion is less than 10% of reactions that require hospitalisation.

The data will also be summarised by "SCENESSE exposure at entry" (3 subgroups), History of asthma [Yes/No] and History of allergies [Yes/No].

Laboratory data

Laboratory samples will only be taken where clinically indicated. For each parameter (haematology, biochemistry, urinalysis), the frequency and percentage of values falling into the three categories (within normal range; outside normal range / not clinically significant; outside normal range / clinically significant) will be summarised at baseline and for each post-baseline visit window for those treated patients (Treatment Group AI) with laboratory sample taken within the visit windows specified (VWI).

Any untreated patient (Treatment Group AII) with a value outside normal range / clinically significant will have that value listed.

All laboratory data will be listed.

<u>Analysis of Clinical Effectiveness</u>

All patients enrolled in the registry will be included in the assessment of clinical effectiveness so long as data are available. In general, baseline will be the data recorded on entry into the Registry. In general, clinical effectiveness will also be summarised by the subgroup variables, SCENESSE exposure at entry and Season of enrolment.

In the assessment of clinical effectiveness, there will be no imputation for "missing data" for the following reasons:

a. Patients may commence treatment at any time independent of season. They are free to choose the timing of treatment provided that treatment does not exceed to frequency and maximum number of doses as defined in the SmPC. Should they choose to receive treatment less frequently than once every two months, data at the designated collection times will be unavailable as opposed to missing. In this situation there would be no requirement to record data
b. The conventional method of imputing based on the last observation carried forward does not take the seasonal nature of EPP into account. The last observation in winter would be

very different to the last observation in summer simply because of seasonality of disease severity

c. To impute on the basis of group data does not take the very large between patient variability into account.

Continuity on treatment

The number of patients who remain on the registry will be summarised in 6 monthly intervals from the entry into the Registry. Treatment Grouping B will be used. That is, (BI + BIII) versus (BII + BIV) reflecting the original decision to receive SCENESSE or not on entry.

Reasons for discontinuation will be summarised at each reporting period. Patients will also be summarised according to the following categories: On Registry, receiving treatment; On Registry, treatment stopped; On Registry, not received treatment to date; Withdrawn, never received treatment; Withdrawn, received at least one dose of treatment.

The number of treated patients who remain complaint will be summarised overall and by 12 monthly time intervals using treatment group AI. A "compliant patient" will be defined as a patient who receives between 3 and 4 doses of SCENESSE in a 12 month time interval (corresponding to Days 0, 60, 120 and possibly Day 180) to allow for patients who enter the registry at different times (i.e. different seasons) during a year. "Full cycle compliance" will also be calculated whereby the number of complete cycles will be calculated for each treated patient, where a full cycle corresponds to 3-4 doses commencing in the Spring of each treated year. The number of patients with complete cycles (0, 1, 2 etc.) will be summarised for treatment group AI using frequencies and percentages.

Quality of Life (EPP-QoL)

The EPP-QoL questionnaire will be completed by the treated patients at baseline prior to treatment in Year 1 and at each subsequent visit. For patients not treated, the questionnaire will be completed at baseline and annually thereafter.

The Total Score (0-100) will be summarised over the study duration including Baseline and post-baseline for those treated patients (Treatment Group AI) with completed questionnaires within the visit windows specified above (VWI). The Total score will be summarised using the mean, median, standard deviation, minimum, maximum and N at each time-point while change from baseline will be summarised using the mean, median, standard deviation, standard error, minimum, maximum and N. Each question (4 point-scale) will also be summarised separately using frequencies and percentages at Baseline and for each post-baseline visit window.

Treatment Grouping B will be used to compare patients on treatment with those not on treatment. That is, (BI + BIII [up until 2m after last dose]) versus (BII + BIV [up until time of first SCENESSE dose] using visit window II. Data will be summarised at Baseline and annually corresponding to VWII and also in terms of change from baseline.

In addition Treatment Grouping B will be used according to the original decision to receive treatment. That is (BI + BIII) versus (BII + BIV), using all data recorded whilst one the registry using VWII.

Daily Activity Inventory

The Daily Activity Inventory will be completed by the treated patients at baseline prior to treatment in Year 1 and at each subsequent visit. In addition, patients' statements on their experience with SCENESSE® will be recorded at the end of each treatment year. For patients not treated, the questionnaire will be completed at baseline and annually thereafter.

The Daily Activity Inventory will be summarised over the study duration including Baseline and post-baseline for those treated patients (Treatment Group AI) with completed questionnaires within the visit windows specified (VWI). Each question will be summarised separately using frequencies and percentages

Treatment Grouping B will be used to compare patients on treatment with those not on treatment. That is, (BI + BIII [up until 2m after last dose]) versus (BII + BIV [up until time of first SCENESSE dose] using visit window II. Data will be summarised at Baseline and annually corresponding to VWII.

In addition Treatment Grouping B will be used according to the original decision to receive treatment. That is (BI + BIII) versus (BII + BIV), using all data recorded whilst one the registry using VWII.

Light and Sun Protection Measures

Light and sun protection measures will be recorded by the treated patients at baseline prior to treatment in Year 1 and at each subsequent visit. For patients selecting not not to be treated, or ineligible for treatment, the questionnaire will be completed at baseline, Day 180 and then twice annually thereafter (corresponding to day 0 and day 180 of each yearly cycle).

The number and percentage of patients that have used measures to protect against light and sun within the last two months will be summarised at baseline and each post-baseline visit.

Use of protective clothing will be summarised for each form of protection (hat, balaclava, long sleeves, long pants, socks, gloves, other) at baseline and at each post-baseline visit with respect to the number and percentage of patients using each form of protection.

Frequency of reflective sunscreen use will be summarised at baseline and at each post-baseline visit using frequencies and percentages according to the following categories (not used, rarely, infrequently, at least once a week, daily).

The number and percentage of patients that have used environment adaptions/visible filters will be summarised at baseline and each post-baseline visit.

The light and sun protection measures will be summarised over the study duration including Baseline and post-baseline for those treated patients (Treatment Group AI) with data available within the visit windows specified (VWI).

All data will be listed, including details of type of sunscreen used and the body location of application.

Phototoxicity

Phototoxicity will be evaluated at baseline prior to treatment in Year 1 and at each subsequent visit. Patients will be asked to report the number and severity of phototoxic reactions experienced. The severity of phototoxic reactions will be recorded in daily diaries to be kept by patients at baseline and then in weeks 1 and 5 following SCENESSE® administration. For patients not treated, the evaluation will be completed at baseline and during summer (notionally listed as Day 120), then twice annually thereafter (corresponding roughly to Day 0 and Day 120).

The number and percentage of patients that experienced any reactions to sunlight and/or light sources (phototoxicity) during the last two months will be summarised at baseline and each post-baseline visit. The number of episodes of phototoxicity (0, 1, 2, 3 etc.) will be summarised at baseline and each post-baseline visit. The length of the patient's worst episode will be summarised in hours (zero hours, if no phototoxicity episode occurred), using the mean, median, standard deviation, minimum, maximum and N.

The phototoxicity measures will be summarised over the study duration including Baseline and post-baseline for those treated patients (Treatment Group AI) with data available within the visit windows specified (VWI).

<u>Summary of Baseline Characteristics and Medical History</u>

All patients enrolled in the registry will be included in the summary of baseline characteristics.

Baseline characteristics and medical history will be summarised by Treatment Grouping B based on the initial patient decision to receive SCENESSE on entry into the Registry. That is, (BI + BIII) versus (BII + BIV). The data will also be summarised by Treatment Grouping A.

Age, Gender, Previously received SCENESSE (on a clinical trial, special access scheme or compassionate use program), Currently receiving SCENESSE, will be summarised using descriptive statistics (frequencies and percentage for categorical data and mean, median, standard deviation, minimum, maximum for continuous data). Medical history will be summarised by each category and whether it is ongoing on entry to Registry.

Medical history related to EPP diagnosis will be summarised separately. Duration of EPP will be calculated in years from year of diagnosis to year of entry to the Registry. The approximate time from light exposure to onset of first symptoms (minutes) will be summarised using the mean, median, standard deviation, minimum and maximum. The frequency and percentage of patients with each troublesome aspect of phototoxity will be summarised as will the family history of EPP. The frequency and percentage of patients where each of the six statements apply with respect to how EPP affected the patient as a child/teenager will be summarised. Similarly for the seven statements with respect to how EPP affected the patient's education and/or professional career.

Medical history related to skin cancer risk factors will be summarised separately using frequency and percentage with respect to: patient currently suffers from a form of skin cancer; patient has suffered from a form of skin cancer in the past; family history of melanoma; Fitzpatrick skin type; eye colour; and, hair colour.

All data will be listed.

Summary of physical examination and vital signs

Physical examination and vital signs are recorded at baseline and annually thereafter.

Baseline data will be summarised by Treatment Grouping B based on the initial patient decision to receive SCENESSE on entry into the Registry. That is, (BI + BIII) versus (BII + BIV). The data will also be summarised by Treatment Grouping A. Patients with an abnormality for each tract will be summarised using frequencies and percentages. Blood pressure, heart rate, temperature, weight and height will be summarised using the mean, median, standard deviation, minimum, maximum and N.

Physical examination abnormalities will also be summarised at each annual visit using frequencies and percentages while vital signs will be summarised at each annual visit and in terms of change from baseline using the mean, median, standard deviation, standard error, minimum, maximum and N. The summaries will be by treatment grouping B – that is, (BI + BIII) versus (BII + BIV). All data will be listed.

Risk minimisation measures:

Changes in cutaneous efflorescence – compliance with 6 monthly full body examination will be assessed by evaluating the number of examinations performed on each patient during a treatment year.

Application site reactions – compliance with the provision of educational material, and the training and accreditation of all physicians who will administer SCENESSE® will be assessed.

Off-label use (in children or adults without EPP) – demographic data and confirmation of EPP diagnosis will be recorded at baseline. The incidence of treated patients who do not comply with the requirements of the SmPC for age or disease status will be determined. Acceptability criteria are:

- No more than 1% of all cases involve off-label use in children
- No more than 5% of all cases involve off-label use in adults

Use in pregnancy or lactation – reports of use during pregnancy or lactation will be collected and followed up and the acceptability criterion is less than 5% of women treated with SCENESSE® become pregnant or breastfeed during treatment.

Administration errors – these will be recorded and the acceptability criterion is that administration errors occur in not more than 5% of administrations.

9.8. Quality control

The study monitor will perform source data verification of data entered into the electronic CRF pages, and raise queries for correction by the institution. This will be done for all sites treating patients. The data entered into the electronic CRF pages will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the institutional staff for response before the database is locked, and released for statistical analysis. More detail on quality control with respect to the disease registry is provided in a separate document entitled “Electronic European EPP Disease Registry”.

9.9. Limitations of the research methods

It is likely that most adult EPP patients will agree to treatment with their data entered into the European EPP Disease Registry database. Conversely, a much lower number agreeing to participate in the Disease Registry but not accepting treatment with SCENESSE® would be expected. This may have an impact on the balance of Treated and Untreated patients but it is also likely that these patients will attend the treatment centre much less often for their EPP so the collection of data will be less frequent. This may reduce the possibility for comparisons between Treated and Untreated Groups.

Clearly, those who choose not to participate in the Disease Registry will not contribute data to the analyses. It is not known what impact this could have on the balance of Treated and Untreated Groups. Based on the experience gained by Clinuvel from 2010 to date in Italy and Switzerland, the number of non-participators is 1 in 98; the number of patients who discontinued treatment was 17, while 13 resumed treatment at a later stage.

The EPP-QoL questionnaire has been partially validated and a full schedule for completion of the validation will be provided separately. The Daily Activity Inventory will also be validated using data generated during the study.

Given the relatively small patient numbers likely to be enrolled, the reliability of longitudinal analyses following treatment discontinuations may not be assessable. Also, the impact of recall on sun protection measures used and phototoxicity may not be controlled for. However, the alternative of continuous daily diary entry over extended periods is likely to lead to poor compliance over time and this would likely yield poorer data and the impact of recall. Hence, diary keeping will only represent a limited part of this protocol.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

This non-interventional study will be conducted in accordance with the relevant national legislation and guidance of those Member States where the study is being conducted. It will also be conducted in accordance with the Declaration of Helsinki, its revisions (Scotland, October 2000 and incorporating Notes of Clarification - Washington, 2002, Tokyo, 2004 and Seoul 2008).

All patients whose pseudonymised data are being uploaded to the Disease Registry will be required to provide written consent to their pseudonymised data being captured, stored and transmitted. Neither the MAH nor any third party contractor will be able to identify any patient based on the information uploaded to the registry. Patients may opt out of having their data shared for research purposes (such as peer-review research outlined below) but are not able to opt out of their data being used for reporting to the EMA.

Prior to any assessment/evaluation, the physician will explain to each patient the nature of the study, its purpose, procedures to be performed, the necessity for withdrawal of prohibited medication, expected duration, and the benefits and risks of study participation. After this explanation and before any assessment/ evaluation is performed, the patient must voluntarily sign an informed consent statement in the Participant Information and Informed Consent in the presence of a witness, if applicable. An appropriate HREC will approve the protocol and the Participant Information and Informed Consent, where applicable with the relevant national legislation and guidance of those Member States where the study is being conducted.

The highest possible standards of professional conduct and confidentiality will be maintained, and legislation and data protection followed as applicable in each individual country.

All study data will be handled and stored to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the patients remains protected. The confidentiality will be assured through password-only access to the registry from individuals authorised through the OpenClinica system, with levels of access depending on the role of the individual in managing and maintaining the registry. Any personal details of subjects will be accessible only to the treating physician and authorised institutional staff.

More information on the registry and the handling of patient data is provided in a separate document entitled “Electronic European EPP Disease Registry”.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

Definitions:

Adverse Event: Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction: A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

All adverse events will be graded for severity as defined below:

- **Mild** - Transient and easily tolerated by the patient. Specific action is optional.
- **Moderate** - The reaction causes the patient discomfort and interrupts the patient's usual activities.
- **Severe** - The reaction causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

Outcome of the adverse event must be described as one of the following:

- Resolved without sequelae
- Resolved with sequelae
- Continuing

All adverse events will be assessed (severity, outcome and causality), from the time of the first SCENESSE® administration, and entered by the physician into the European EPP Disease Registry database. These will be sent electronically to the QPPV for processing and onward reporting as required. A pharmacovigilance service provider has been commissioned by the MAH to provide pharmacovigilance QP and related services.

Serious Adverse Event (SAE): A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or

- is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Reporting: Any SAE, including death due to any cause, which occurs must be reported by telephone to the MAH **within 24 hours** of knowledge of the event. In addition to this initial report, a Serious Adverse Event form will be completed and sent via facsimile or email to the MAH.

The Lead Physician will determine whether the seriousness of the event warrants discontinuation of treatment with SCENESSE®. The Physician will institute appropriate diagnostic and therapeutic measures and keep the patient under observation for as long as is medically indicated. The European EPP Disease Registry has been designed to alert the QPPV, the MAH and the Data and Safety Monitoring Board (DSMB) of SAEs. Regular data exports from the registry will be transmitted to the QPPV for analysis and appropriate reporting to the EMA. Safety data forming part of the interim results from the study and PSURs will be prepared by the QPPV and reviewed by the MAH/DSMB prior to submission to the EMA and PRAC.

The DSMB will consist of at least one independent medical expert appointed by the MAH. The DSMB will receive regular safety reports from the QPPV and from the registry. In the event of an SAE, the DSMB is expected to speak with both the MAH and the EPP expert centre which reported the SAE within 24 hours of its report. The DSMB will have the power to request a recall of the product in the event of safety concerns identified via the registry. Formal contracts between DSMB and the DSMB members will outline Terms of Reference and the agreed roles.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of the formal analyses will be made available to all treatment centres. Formal arrangements for publication of results will be finalised after all treatment centres have been recruited.

All interim reports will be made available to the competent authorities.

Any safety concerns that may be identified during interim analyses will be immediately communicated to all participating physicians following review by the DSMB. These safety concerns will also be immediately notified as emerging safety issues in writing to the competent authorities in Member States where the medicinal product is authorised and to the Agency.

13. REFERENCES

Not applicable other than the references provided in clinical study reports for the CUV029, CUV030 and CUV039 studies.

APPENDIX G (1): STUDY PROCEDURES MATRIX FOR TREATED PATIENTS

Study Procedure	Baseline / Dose 1*	Year 1			Years 2 and After			
		Day 60@ Dose 2	Day 120@ Dose 3	Day 180@# Dose 4	Baseline / Dose 1	Day 60@ Dose 2	Day 120@ Dose 3	Day 180@# Dose 4
Informed consent taken	X							
ROUTINE MONITORING								
Demographic information collected	X							
Medical history taken	X							
General physical examination	X				X			
Vital signs	X				X			
Weight / height measurement	X[3]				X			
Quality of life assessment (EPP-QoL) [6,9] Daily activity inventory[6,9]	X	X	X	X	X	X	X	X
Patients' statements[6]			X[5]	X[5]				
Sun protection measures[6,9]	X	X	X	X	X	X	X	X
Phototoxic reaction review[6,9]	X	X	X	X	X	X	X	X
Adverse events review following all administrations and 2 months after the last administration in all treatment years[6]	X	X	X	X	X	X	X	X
Concomitant medication review[6]	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review[6]	X	X	X	X	X	X	X	X
SCENESSE® administration[2, 6]	X	X	X	X	X	X	X	X
GASTROENTEROLOGIST								
Physical examination, abdominal palpation, percussion and auscultation	X				X			

Ultrasound liver	X				X			
DERMATOLOGIST								
Skin cancer risk factor questions completed	X							
Full body topography, skin and oral mucosal examination[7]	X			X	X			X
PHOTOGRAPHY[4]								
Full body photography[8]	X			X	X			X
ADDITIONAL MONITORING[1]								
Hematology and blood chemistry[1]	X	X	X	X	X	X	X	X
Urinalysis[1]	X	X	X	X	X	X	X	X
Vital signs[1]	X	X	X	X	X	X	X	X

@ Notional days only for planning purposes – the visits closest to these dates should be used in assessments

Optional if the treating physician considers a fourth dose necessary

* Baseline assessments performed and evaluated prior to the first administration

1 Haematological and biochemical parameters as available through routine clinical practice except for patients over 70 years whose haematological and biochemical parameters should be closely monitored after each administration of SCENESSE®

2 SCENESSE® administration only after confirmation that female patients are using effective contraceptive methods

3 Height will be measured at Visit 1 only to allow calculation of BMI

4 Anterior and posterior photography as per instructions provided

5 Only at the time of the last annual scheduled dose, either the third or fourth annual dose, as appropriate. If uncertain whether 3 or 4 doses will be administered, statements should be taken at the third annual dose, as a minimum.

6 All evaluations to be performed at the same times during year 2 and subsequent treatment years

7 Full body topography, skin and oral mucosal examination to be performed every six months in all treatment years

8 Data should be collected as available from routine practice

9 For patients who receive an optional fourth dose, arrangements will be made to collect effectiveness data following this dose

APPENDIX G (2): STUDY PROCEDURES MATRIX FOR UNTREATED PATIENTS

Study Procedure	Baseline	Year 1			Years 2 and After[4]			
		Day 60[@]	Day 120[@]	Day 180[@]	Baseline	Day 60[@]	Day 120[@]	Day 180[@]
Informed consent taken	X							
ROUTINE MONITORING								
Demographic information collected	X							
Medical history taken	X							
General physical examination	X				X			
Vital signs	X				X			
Weight / height measurement	X[2]				X			
Quality of life assessment (EPP-QoL) Daily activity inventory	X				X			
Sun protection measures	X		X		X		X	
Phototoxic reaction review	X		X		X		X	
Adverse events review	X				X			
Concomitant medication review	X				X			
GASTROENTEROLOGIST								
Physical examination, abdominal palpation, percussion and auscultation	X				X			
Ultrasound liver	X				X			
DERMATOLOGIST								
Skin cancer risk factor questions completed	X							
Full body topography, skin and oral mucosal examination[5]	X				X			

PHOTOGRAPHY[4]								
Full body photography[3]	**X**				**X**			
ADDITIONAL MONITORING[1]								
Hematology and blood chemistry[1]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urinalysis[1]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital signs[1]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

@ Notional days only for planning purposes – the visits closest to these dates should be used in assessments

1 Only if clinically indicated and with data collected only as available from routine practice

2 Height will be measured at Visit 1 only to allow calculation of BMI

3 Anterior and posterior photography as per instructions provided with data collected only as available from routine practice

4 All evaluations to be performed at the same times during year 2 and subsequent treatment years

5 Full body topography, skin and oral mucosal examination to be performed every six months in all treatment years